78. (New) The compound of claim 77 wherein the modified internucleoside linkage is a phosphorothioate linkage.

79. (New) The compound of claim 76 wherein the oligonucleotide mimetic compound comprises at least one modified sugar moiety.

80. (New) The compound of claim 79 wherein the modified sugar moiety is a 2'-O-methoxyethyl sugar moiety.

81. (New) The compound of claim 76 wherein the antisense oligonucleotide comprises at least one modified nucleobase.

82. (New) The compound of claim 81, wherein the modified nucleobase is a 5-methylcytosine.

83. (New) The compound of claim 76 wherein the oligonucleotide mimetic compound is a chimeric oligonucleotide.

REMARKS

Claims 1, 12, 15, and 71 are amended herein. Claims 72-83 are newly added. The amendments and new claims do not represent new matter.

Claim 1 is amended to clarify with what the compound hybridizes. Furthermore, claim 1 is amended to specify a percentage of inhibition as measured in a specific assaying method. New claims 72-75 further limit the percentage inhibition of expression. Support for the amendments to claim 1 and for new claims 72-75 can be found throughout the specification, including at least at pages 89 and 90.

Applicant also adds claims 76-83. Support for the subject matter of these claims can be found throughout the specification, including at least at pages 12-22.

Applicant also amended claims 12 and 15 to depend from new claim 76.

II. RESPONSE TO THE OFFICE ACTION OF JANUARY 14, 2003

A. The Status of the Claims

Claims 1, 2, 4-15, and 71 stand rejected.

Claims 1, 12, 15, and 71 are amended herein.

Claims 72-83 are newly added.

Thus, claims 1, 2, 4-15, and 71-83 are currently pending.

B. The Outstanding Rejections

Claim 11 stands rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for reciting the term "active site."

Claim 71 stands rejected under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 15 and 71 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly not enabled by the specification.

Claims 1, 2, 4-8, and 11-15 stand rejected under 35 U.S.C. § 102(a) as allegedly anticipated by Mitchell *et al.*

Claims 1 and 2 stand rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Holst *et al.* and Langin *et al.*

Claims 1, 2, 4-14 stand rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Mitchell *et al.*, Holst *et al.*, and Langin *et al.* in view of Barracchini *et al.*

C. Patentability Arguments

1. The Rejection under 35 U.S.C. § 112, second paragraph, Should be Withdrawn

Claim 11 stands rejected as allegedly indefinite for use of the term "active site," however, no analysis is given by the Examiner as to why the term is "vague and unclear." Nonetheless, Applicant respectfully submits that the use of the term "active site" in claim 11 does not render the claim indefinite.

"The test for definiteness under 35 U.S.C. 112, second paragraph is whether 'those skilled in the art would understand what is claimed when the claim is read in light of the

specification.'" MPEP § 2173.02 quoting *Orthokinetics, Inc. v. Safety Travel Chairs, Inc.*, 806 F.2d 1565, 1576, 1 USPQ2d 1081, 1088 (Fed. Cir. 1986). Applicant points the Examiner's attention to the present specification at page 10, lines 7-15, which explains the meaning of the term "active sites," and page 90, lines 3-10, which provides examples of "active sites." It is respectfully submitted that, when claim 11 is read in light of the specification, those skilled in the art would understand what the term "active site" encompasses. Thus, the rejection of claim 11 under 35 U.S.C. § 112, second paragraph, should be withdrawn.

2. The Rejection under 35 U.S.C. § 112, first paragraph, for Lack of Written Description Should be Withdrawn

One of ordinary skill in the art would recognize that the inventors invented what is claimed. Claim 71 is directed to a compound 8 to 50 nucleobases in length targeted to a nucleic acid molecule encoding human hormone-sensitive lipase (SEQ ID NO: 3), wherein said compound specifically hybridizes with and inhibits the expression of a nucleic acid molecule encoding an alternatively spliced form of hormone-sensitive lipase. The specification is replete with indicators of the inventors' possession of the claimed invention at the time of filing.

Claim 71 is an original claim and, as such, is part of the original disclosure. As discussed on page 2 of the present specification, an alternatively spliced form of human hormone-sensitive lipase (hsl) was known in the art at the time of filing. (See Holst *et al.*, 1996). The sequence of the alternatively spliced form is provided as SEQ ID NO:17. Example 15 describes the designing of nucleotides to target different regions of the alternatively spliced human hsl RNA (See column 3 of Table 1). Furthermore, it would be understood by one of ordinary skill in the art that, because the alternatively spliced forms of human hsl share extensive overlapping of sequence, many compounds that target one form would target both forms. Thus, as evidenced by the original claims and disclosure, particularly the disclosure of specific compounds directed to alternatively spliced forms of human hsl, one of ordinary skill in the art would recognize that the inventors were in possession of the invention of claim 71 at the time of filing.

The Office Action rejects the claims on the basis that the sequences of any and/or all alternatively spliced forms of human hsl are not described in the specification and claims.

Applicant respectfully traverses. As discussed above, the sequences of alternatively spliced hsl RNA are disclosed in the specification and the specification discloses numerous compounds that are targeted to inhibit expression of each RNA (see, for example, Table 1 of specification). Based on the present disclosure, one of ordinary skill in the art could recognize that the inventors were in possession of compounds 8 to 50 nucleobases in length targeted to the alternatively spliced form, which function in the manner claimed. The disclosure therefore provides an adequate description of the genus claimed, demonstrating the Applicant was in possession of the invention at the time of filing. Accordingly, the rejection of claim 71 under 35 U.S.C. § 112, first paragraph, for lack of written description should be withdrawn.

3. The Rejection under 35 U.S.C. § 112, first paragraph, for Lack of Enablement Should be Withdrawn

Claims 15 and 71 stand rejected as assertedly not being enabled by the specification. Applicant respectfully traverses and provides the following discussion for the Examiner's consideration.

a. The specification provides express working examples of how to make and use the claimed invention

Claim 15 is directed to a method of inhibiting the expression of hsl in cells or tissues comprising contacting the cells or tissues with the compound of claim 1 (or claim 76 as amended) so that expression of hsl is inhibited. Example 9 provides exemplary cell lines and methods of determining the optimal oligonucleotide concentration for a given cell line. Examples 9, 13 and 14 provide exemplary methods of assaying hsl expression. Example 16 demonstrates that a compound of claim 1 inhibits expression of hsl in cells contacted in culture.

Using a compound that is completely complementary to sequences in the human and mouse hsl, the specification demonstrates that a compound of claim 1 inhibits expression of hsl in cells contacted *in vivo*. One such compound (ISIS 126930) was able to decrease hsl expression in liver of ob/ob mice receiving intraperitoneal (IP) injection of the compound (Example 20) and in liver of the P-407 murine model of hyperlipedemia (Example 28). Thus, in one aspect, IP administration allows contacting of liver cells with a compound of the invention, which results decreased expression of hsl.

Pages 27-54 provide an extensive description of local and systemic administration routes, along with exemplary formulations for the various administrative routes. Using the specification as a guide and routine experimentation, one of ordinary skill in the art would understand how to optimize formulation and administration of a compound of claim 1 (and claim 76 as amended) in order to contact a cell or tissue with the compound such that expression of hsl is inhibited.

Regarding the rejection of claim 71, Applicant incorporates by reference the discussion above regarding the inventors' possession of the invention of claim 71 at the time of filing. Because the specification indicates that the inventors were in possession of the invention of claim 71 at the time of filing, it is corollary that the specification enables the invention of claim 71. *Moba,* (J. Rader dissent) ("After all, to enable is to show possession and to show possession is to enable."). The rejection fails to put forth any evidence to suggest that it would require undue experimentation to make and use the compound of claim 71 despite the extensive teachings of the specification.

b. The art cited in the rejection supports the express teachings of the specification

The rejection puts forth a number of publications in an effort to support the assertion undue experimentation would be required to make and use the inventions of claims 15 and 71. However, taken as a whole and individually, the cited art fails to call into question the express teachings of the specification. In fact, the cited references support the position that, using the specification as a guide, one of skill in the art could make and use the invention of claims 15 and 71 with nothing more than routine experimentation.

The Branch article asserts that (i) not all regions of a target RNA are vulnerable to antisense inhibition (pp. 48-49, See "The three As..."); (ii) the intricate structure of an RNA *in vivo* renders only certain areas susceptible; and this characteristic often renders "in test tube" methods unpredictable. (Please note that in the Branch article *in vivo* is used in the context of "in cell" and not as "in the body."). As discussed above, however, the specification provides working examples of "in cell" methods of screening for "active sites" in target nucleic acids that are accessible to the compounds of the present invention. Once these accessible "active" sites are found, there is nothing in Branch that suggests these

molecules would not target expression of hsl in cells contacted by the compounds "in the body."

The Crooke reference is a review discussing the state of the art of antisense technology in 1998 and the rejection relies on Crooke to assert that cell culture examples are generally not predictive of *in vivo* inhibition of target genes. Regardless of this interpretation, the present specification teaches *in vivo* assays for determining inhibition of hsl in cells contacted with a compound of claim 1, which was in fact identified by initial screening with a cell culture system.

Taken as a whole and contrary to the Examiner's assertion, Crooke demonstrates that, although certain aspects of the technology may be unpredictable in regards to pharmacology, antisense technology works. Crooke provides many examples of gene targeting in a number of cell and tissue types through a number of administration routes. (See page 20, second full paragraph; page 22-26, particularly Table 1). There is nothing in Crooke that suggests that contacting of cells or tissue with a compound of claim 1 should be limited to only the exemplified route.

The art cited in the rejection pertaining to the efficacy of antisense technology in treating disease is immaterial to the present claims. (BioWorld Today; Palu et al., Agrawal et al.; and Chirila et al.). The BioWorld Today article did not indicate that the administered compound failed to contact cells and inhibit expression of ICAM-1, it only indicates that the patients did not show the desired therapeutic effect. Agrawal acknowledges that cellular uptake of antisense molecules *in vivo* is **less** restrictive than in the *in vitro* setting. (See pp. 79-80, "Cellular uptake..."). Furthermore, pages 326-327 of Chirila merely indicate that often repeated administration of antisense molecules is needed to achieve a **therapeutic** effect. (See p. 327, last paragraph). In fact, Chirila confirms that antisense molecules may be administered by a number of routes including intraveneous infusion, subcutaneous injection, and intramuscular injection. (p. 327, second complete paragraph).

There is nothing in the cited art to indicate that optimizing administration routes requires undue experimentation. Indeed, the art confirms that those of skill in the art were aware multiple delivery routes are available and that each route may require efficacy optimization. Using the specification as a guide, one of ordinary skill in the art would understand how to determine if a particular administration route meets the claim limitation of contacting cells or tissues so that expression of hsl is inhibited.

c. The rejection for lack of enablement is incorrect as a matter of law as set forth by the Federal Circuit and as discussed in the MPEP

The rejection would require the inventors to disclose molecules that inhibit any and/or all spliced forms of hsl, to provide examples of such *in vitro* and *in vivo*, and to demonstrate administration by any and/or all routes.

Applicant objects to the above rejection as applying the wrong standard for enablement. The enablement requirements of the statute are satisfied when the specification disclosure, taken with the teachings in the art, teaches an effective process for making and using the claimed compounds from know starting materials, and the specification describes methods of using the claimed compounds. *Ex parte Gastambide, Thal, Rohrbacj and Laroche*, 189 USPQ 643, 645 (PTO Bd. App. 1974). Thus, all that is required is that the Applicant objectively enable the claimed invention. The law has never required that the Applicant provide specific working examples.

The time and the difficulty of experiments that are needed are not determinative to enablement if they are merely routine. MPEP § 2164.06. MPEP § 2164.01(b) provides specific examples in the case law of decisions ruling that the disclosure was either non-enabling or enabling. Under the former category, the MPEP cites a number of decisions including *In re Wright*, 999 F.2d 1557, 27 USPQ2d 1510 (Fed. Cir. 1993); and *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993). The latter category cited, among other decisions, *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1999) and In re Bundy, 642 F.2d 430, 209 USPQ 48 (CCPA 1981). The facts and analysis of the present case are more akin to *In re Wands* and *In re Bundy* than to *In re Wright* and *In re Goodman*.

In both *In re Wright* and *In re Goodman* there was **specific** evidence that cast doubt on the scope of the claimed invention. For example, in *In re Wright*, the Examiner provided a teaching from the art that compositions of the claimed scope "...remained an intractable problem" and that "this evidence, along with the evidence that RNA viruses were a diverse and complicated genus" led the Federal Circuit to conclude that the invention was not enabled. **That is not the case here**. The rejection fails to put forth any specific evidence showing that inhibition of expression of genes *in vivo* is an "intractable problem." Furthermore, no specific evidence is provided showing that alternatively spliced forms of hsl constitute a "diverse and complicated genus."

The facts of the present case are more akin to *In re Wands,* wherein the court indicated that the sole issue in that case was "whether it would require undue experimentation to produce high-affinity IgM monoclonal antibodies." The court specifically noted that no undue experimentation is required to practice an invention if the material being claimed can be made from readily available starting material through routine screening. *Id.* at 739. The court stated that the nature of hybridoma technology involved an extensive amount of screening and practitioners in that art are prepared for such screening. *Id.* Here, even if screening and optimizations are required, those of skill in the art, as indicated by the references cited in the rejection, are prepared for such screening and optimization procedures.

As Applicant has previously discussed, the specification provides express working examples of how to make and use the claimed inventions, the art cited by the rejection supports the express teachings of the specification, and the rejection is incorrect as a matter of law. Because the experimentation required to practice the full scope of the method of claim 15 and to make and use the compound of claim 71 is merely routine, the rejection of claims 15 and 71 under 35 U.S.C. § 112, first paragraph, for lack of enablement should be withdrawn.

4. The Rejections under 35 U.S.C. § 102 Should be Withdrawn

Claims 1, 2, 4-8, 11-15 stand rejected under 35 U.S.C. § 102(a) as allegedly being anticipated by Mitchell *et al.* Applicant respectfully traverses the rejection.

Mitchell *et al.* discloses the sequence of the alternatively spliced form of hsl expressed in testes. As one of a number of alternative approaches to down-regulate the expression of hsl, Mitchell proposes antisense molecules. However, not a single antisense molecule is disclosed. Because Mitchell merely discloses a sequence of a gene and suggests antisense technology as a method of inhibiting expression of the gene, Mitchell does not anticipate the compounds of the claims.

Even if Mitchell could be said to disclose antisense molecules, it does not disclose the compounds of the rejected claims. The rejected claims were directed to compounds **8 to 50** nucleobases in length that specifically hybridize with and inhibit the expression of human hsl (and methods using such compounds (claim 15)). Mitchell, on page 8, states "antisense oligonucleotides in accordance with this invention may **comprise** from about **5 to about 100 nucleotide units**," i.e., about 5 or more nucleotide units. This is an extremely broad range of

length. Although the claimed compounds fall within this broad range, no specific examples falling within the claimed range are disclosed by Mitchell. According to MPEP § 2131.03, "In order to anticipate the claims, the claimed subject matter must be disclosed in the reference with 'sufficient specificity to constitute an anticipation under the statute.'" Applicant respectfully submits that a reference disclosing a gene sequence and wishing for antisense molecules greater than 5 nucleotide units cannot be said to disclose, with "sufficient specificity to constitute an anticipation," compounds 8 to 50 nucleobases in length that hybridize and inhibit the expression of hsl. Moreover, Mitchell does not disclose compounds that inhibits expression of hsl in the HepG2 assay to the extent presently claimed.

Claims 1 and 2 stand rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Holst *et al.* Applicants respectfully traverse the rejection. As amended herein, claim 1 (and claim 2) specify a percent inhibition as measured in a specific assaying method. Holst does not disclose, and the Examiner provides no rationale or evidence showing, that the primer disclosed in Holst inhibits expression of hsl, which is a functional limitation of the claims, particularly to the extent in the HepG2 assay presently claimed.

Similarly, claims 1 and 2 stand rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Langin et al. Applicants respectfully traverse the rejection. As amended herein, claim 1 (and claim 2) recite a percent inhibition as measured in a specific assaying method. Langin does not disclose, and the Examiner provides no rationale or evidence showing, that the primer disclosed in Holst inhibits expression of hsl, which is a functional limitation of the claims, particularly to the extent in the HepG2 assay presently claimed.

Because the references cited against the pending claims fail to teach each and every limitation of the claims, the cited references cannot anticipate the subject matter of the pending claims. The rejection under 35 U.S.C. § 102 should be withdrawn.

5. The Rejection under 35 U.S.C. § 103 Should be Withdrawn

Claims 1, 2, and 4-14 stand rejected as allegedly unpatentable over Mitchell, Holst, and Langin in view of Baracchini. Applicant respectfully traverses the rejection.

As discussed above, the primary references do not disclose compounds 8 to 50 nucleobases in length that specifically hybridize with and inhibit expression of hsl, particularly to the extent in the HepG2 assay presently claimed. The teaching of Baracchini to incorporate 5 methyl cytosines and chimeric structures into antisense oligonucleotides

directed to multidrug resistance-associated protein does not overcome this deficiency. Thus, the references, alone or in combination, fail to disclose each and every limitation of the claims. Because the rejection fails to make a *prima facie* case of obviousness, the rejection under 35 U.S.C. § 103 should be withdrawn.

D. Conclusion

In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to withdraw the outstanding rejection of the claims and to pass this application to issue. The Examiner is invited to contact the undersigned attorney at the number listed below with any questions of form or substance.

Dated: May 14, 2003

Respectfully submitted,

By _____

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